

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> A61K 9/50, 9/10, 9/14 B01J 13/02, A23L 1/30	<b>A1</b>	<b>(11) International Publication Number:</b> WO 91/06292 <b>(43) International Publication Date:</b> 16 May 1991 (16.05.91)
<b>(21) International Application Number:</b> PCT/DK90/00278 <b>(22) International Filing Date:</b> 2 November 1990 (02.11.90)  <b>(30) Priority data:</b> 5462/89 2 November 1989 (02.11.89) DK  <b>(71) Applicant (for all designated States except US):</b> DANOCHE-MO A/S [DK/DK]; Malmparken 5, DK-2750 Ballerup (DK).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> MUSAEUS JENSEN, Nina [DK/DK]; Højsgårds Allé 47, DK-2900 Hellerup (DK). VILSTRUP, Per [DK/DK]; Schlepegrellsgade 6, DK-2200 København N (DK). WINNING, Marianne [DK/DK]; Rypevænget 108, DK-2980 Kokkedal (DK).		<b>(74) Agent:</b> LEHMANN & REE; Frederiksberg Allé 26, DK-1820 Frederiksberg C (DK).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU, US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PROCESS OF PREPARING A WATER DISPERSIBLE HYDROPHOBIC OR AEROPHILIC SOLID		
<b>(57) Abstract</b>  Process of preparing a hydrophobic/aerophilic solid which can be dispersed in water in the form of discrete microparticles, wherein the solid is milled in an aqueous medium in the presence of a hydrocolloid to obtain a suspension containing suspended particles of an average particle size not exceeding 10 µm and finely dividing and drying the suspension to obtain a powder.		

BEST AVAILABLE COPY

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Faso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	SD	Sudan
CF	Central African Republic	KP	Democratic People's Republic of Korea	SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Licchtenstein	SU	Soviet Union
CI	Côte d'Ivoire	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

Process of preparing a water dispersible hydrophobic or aerophilic solid.

---

5 The present invention relates to a process of preparing a hydrophobic or aerophilic powdered solid which is dispersible in water or in an aqueous solution (in the following referred to as a water dispersible solid) in the form of discrete microparticles.

10 More specifically the invention relates to a process of preparing water dispersible hydrophobic or aerophilic powdered colorants and biologically active solids.

15 It is well known that the coloring effect of a colorant or pigment dispersed in an aqueous medium increases with decreasing particle size of the colorant or pigment and that the color intensity of the dispersion increases with increasing dispersability.

20 It is also well known that the bioavailability of biologically active powdered solids, such as carotenoids and drugs, such as griseofulvin, ibuprofen, benzodiazepines and hormones, such as progesteron dispersed in an aqueous medium increases with decreasing particle size of the dispersed solid.

25 Therefore, there is a need for providing water dispersible hydrophobic or aerophilic solids of a small particle size, e.g. a particle size not exceeding 10  $\mu\text{m}$  and more preferably not exceeding 2  $\mu\text{m}$ .

30 Various methods of reducing the particle size of hydrophobic/-aerophilic compounds to a maximum average of 10  $\mu\text{m}$  have been disclosed. It is known to mill  $\beta$ -carotene together with edible oil in a colloid mill (Chimia 21, 329 (67)). Using this method it is possible to achieve a  $\beta$ -carotene content in the oil of about 30%.

35 Published Japanese patent application No. 57-3861 discloses a process for preparation of a water-dispersible carotenoid formulation which comprises mixing and grinding a carotenoid with gum arabic in a dry state using a grinding apparatus, such as rotary ball mills, vibration ball mills, and hammer mills. Following

grinding the solid product can be dissolved in water and the resulting solution can be converted into a powder by spray drying or freeze drying. A powder formulation having a carotenoid content of 1.5 percent by weight is obtained. A disadvantage of this method is that the milled compounds may be damaged due to the increase of temperature during grinding or milling in the dry state because of the lack of efficient cooling equipment. Furthermore, it is difficult to prevent oxidation of the milled compounds during a dry grinding or milling operation.

10

Moreover, Chimia 21, 329 (1967), DE application No. 12 11 911 and DE publication No. 25 34 091 disclose a method of dissolving the active compound in a chlorinated organic solvent, emulsifying the solution in a gelatine/sucrose solution and extracting the solvent from the emulsion causing the active compound to crystallize in microcrystalline form. A disadvantage of this method is that it is technically impossible to remove the organic solvent completely and the solvent is a potential hazard during the process and as residues in the final product.

20

DK-B-154.395 discloses a preparation, which has been prepared by dissolving a carotenoid or a retinoid in an organic solvent that is miscible with water at a temperature of between 50 and 200°C optionally under pressure in less than 10 sec. The resulting molecular-disperse solution is immediately mixed with an aqueous solution of a hydrocolloid followed by an isolation of the colloid-disperse particles from the solvent to obtain a dry free flowing powder that can be dispersed in water. This method is disadvantageous because of the use of organic solvents that require special equipment for collection of the solvents. Furthermore, the concentration of the active compound will be relatively low in the final product, i.e. a maximum of about 20 percent by weight. Furthermore, it is stated that it has not been possible to mill hydrophobic solids, such as  $\beta$ -carotene in water or in an aqueous system to obtain the desired particle size without damage to the active compounds.

35

It is well known that an aqueous dispersion of particles of hydrophobic/aerophilic solids can be prepared by mixing a hydrophobic/aerophilic solid with water in the presence of a wetting

agent or tenside, such as lauryl sulfate or polysorbate. Without the use of a wetting agent milling is impossible, and without sufficient wetting the particles will agglomerate and the suspension will become too viscous for milling.

5

The object of the invention is to provide a process for preparing a hydrophobic/aerophilic solid that can be dispersed in water in the form of discrete microparticles without the use of oils, organic solvents and/or wetting agents or similar additives to form a  
10 microencapsulated product having a concentration of up to 71% of hydrophobic aerophilic solid and to provide a microencapsulated product having a concentration of from 22 to 71% of solid active material.

15 This object can be achieved by the process of the invention which process is characterized in that the solid is milled in an aqueous medium in the presence of a hydrocolloid to obtain a suspension containing suspended particles of an average particle size not exceeding  $10\mu\text{m}$  and the suspension thus formed is finely divided and  
20 dried to form a powder.

It is assumed that the hydrocolloid, such as gelatine, provides sufficient wetting of the hydrophobic/aerophilic material to avoid agglomeration of the fine particles formed during the milling  
25 process.

It is assumed that the hydrocolloid protects the new surfaces resulting from the milling of the relatively coarse particles of the hydrophobic/aerophilic material by creating a thin film that is  
30 intimately bound to the reactive new surfaces, thus preventing the particles to agglomerate due to hydrophobic interactions. Furthermore, the hydrocolloid reduces the surface tension and increases the dispersability of the final product.

35 Moreover, the hydrocolloid protects the milled particles in both the liquid and the dried state, thus preventing recrystallisation and crystal growth of materials, such as low melting hormones, low melting lipids and other fat soluble materials.

The milling is preferably effected in a bead mill or any similar mill having cooling equipment for maintaining the temperature below a value at which the hydrofobic/aerophilic materials are decomposed and wherein the materials can be kept under a controlled atmosphere.

5

In a preferred embodiment of the process according to the invention the hydrophobic/aerophilic solid is preferably added to an aqueous solution of a hydrocolloid that has been degassed by boiling under vacuum and preferably covered by N<sub>2</sub> or any other inert gas. The mixture is then stirred at a temperature of between 0°C and 100°C, the lower limit being determined by the temperature at which the hydrocolloid forms a gel and the upper limit being determined by the heat lability of the active compound. Antioxidants may be added to the suspension.

15

The suspension is transferred to the mill which can be any type that is capable of milling the solid to a maximum particle size of 10µm, is equipped with a cooling jacket and wherein the atmosphere can be controlled. During the milling the temperature is between 0°C and 100°C, preferably above 60°C and the pressure is preferably between 0 and 5 bar. The suspension may be pumped through the mill in a peristaltic pump or using a gear pump having a flow of from 50 to 1000 ml/min, preferably from 150 to 400 ml/min.

25

Solid hydrophobic/aerophilic materials that can be milled and encapsulated in the process according to the invention include carotenoids, such as β-carotene, annatto, bixin, norbixin, capsanthin, capsorubin, lycopene, β-apo-8'-carotenal, flavoxanthin, lutein, cryptoxanthin, rubixanthin, violaxanthin, rhodoxanthin, canthaxanthin, astaxanthin and citranaxanthin and derivatives thereof; natural colorants, such as curcumin, chlorophyll, carmine, etc.; and drugs, such as griseofulvin, ibuprofen, benzodiazepines, phenacetin and hormones.

30

Hydrocolloids that can be used in the process according to the invention include exudates, such as gum arabic, tragacanth, gum karaya, gum ghatti; extracts from seaweed, such as agar, alginate, carrageenan and furcellaran; extracts from plants, such as pectin and arabinogalactan; extracts from marine and terrestrial animals,

35



such as gelatines and other proteinaceous hydrocolloids; flours from seeds, such as guar, locust bean, soya bean; proteins from seeds, such as soya bean protein; flours from cereals, such as starches and microcrystalline cellulose; biosynthetic or fermentation derived hydrocolloids, such as dextran, xanthan and curdlan; chemically modified hydrocolloids, such as cellulose derivatives, including methyl cellulose, and other derivatives, including modified starches and low methoxyl pectin; synthetic hydrocolloids, such as polyvinylpyrrolidon, carboxyvinyl polymers, etc.

10

The amount of hydrocolloid used in the process according to the invention is usually not less than 5 percent by weight of the hydrophobic/aerophilic solid, preferably not less than about 10-15 percent by weight of the hydrophobic/aerophilic solid. The required minimum amount of the hydrocolloid to provide sufficient wetting of the solid is dependent on the specific solid and hydrocolloid and the presence of other excipients.

15

The aqueous medium can optionally further contain excipients in an amount of up to 70 percent by weight of the suspension, such as a dissolved carbohydrate, such as sorbitol and sucrose, and/or an antioxidant or an oil containing an antioxidant.

20

The resulting suspension is finely divided and dried using any combination of conventional methods, such as spray cooling, spray drying, modified spray drying or sheet drying and crushing, etc.

25

Another advantage of the process according to the invention is that the hydrocolloid used in the milling of a hydrophobic/aerophilic solid can act as a matrix material in a subsequent encapsulation process. Such processes will be described in the following.

30

#### Spray cooling

In a spray cooling process a suspension containing a hydrocolloid is preferably sprayed using an atomizing nozzle or an atomizing wheel at a temperature higher than the gelling/melting point, i.e. from about 38° to about 95°C and at a viscosity of preferably between 50 and 300 mPa·s in a spraying chamber, wherein the temperature is from

35

0° to about 40°C, thereby forming microcapsules of gelatinized hydrocolloid.

5 A powdery spraying excipient is preferably blown into the spraying chamber in order to prevent agglomeration of the gelatinized microcapsules and to prevent adherence to the chamber wall. The spraying excipient is preferably supplied in an amount of from 5 to 50 percent by weight based on the weight of the final product.

10 The microcapsules are transferred to a fluidized bed, wherein they may be dried to a residual water content of between 0 and 10% (preferably from 2 to 5%) and in which excessive spraying excipient is separated. The drying air temperature is preferably from about 0° to about 60°C.

15

#### Modified spray drying

The modified spray drying process differs from the spray cooling process in that the temperature in the spraying chamber is high, preferably between 50° and 95°C.

20

In the modified spray drying process the suspension is preferably sprayed at a temperature of from 5° to 99°C and at a viscosity of from 50 to 300 mPa·s using an atomizing nozzle or an atomizing wheel in a spraying chamber, wherein the temperature is from 50° to 95°C.

25

A powdery spraying excipient may be blown into the spraying chamber in order to prevent agglomeration of the formed microcapsules and to prevent adherence to the chamber wall. The spraying excipient is preferably supplied in an amount of from 5 to 50 percent by weight based on the weight of the final product.

30

The powdered microcapsules may be transferred to a fluidized bed, wherein they may be dried to a residual water content of between 0 and 10% (preferably from 2 to 5%) and excessive spraying excipient is separated. The drying air temperature is preferable from about 0° to about 60°C.

35

In the spray cooling, spray drying and modified spray drying



processes the following spraying excipients may be used: starches, modified starches, tricalcium phosphate, lactose, mannitol, ethyl cellulose, coagulated albumin, hardened gelatine, casein, stearat-Ca, stearat-Na, metal soaps, hydrogenated ricinus oil, polyoxide, talcum, waxes, and silicates.

In a sheet drying process the suspension is preferably dried in a thin layer to form a solidified suspension which subsequently may be ground into a powder. Alternatively, the suspension may be emulsified in an oil, washed and dried/spray dried or extruded, drum dried and crushed or treated by any combination of known methods of finely dividing and drying or drying and finely dividing.

Microencapsulated  $\beta$ -carotene may be a constituent of vitamin tablets. However, because of the relatively low concentration of  $\beta$ -carotene in microcapsules prepared using the known techniques, it is necessary to formulate the vitamin tablets with a relatively large amount of  $\beta$ -carotene microcapsules resulting in bulky tablets. This obstacle is overcome when tablets are formulated with microcapsules having a high  $\beta$ -carotene content that are prepared according to the invention.

Another advantage of the hydrocolloid protection of microparticles of hydrophobic/aerophilic compounds, such as phenacetin, is an improved performance when preparing tablets from such compounds.

It is preferred to include an antioxidant in the suspension when the active compound is sensitive to oxygen. The antioxidant can be water soluble or water insoluble and can be incorporated during the milling process or in a subsequent emulsification process.

The dispersability of the microencapsulated product is evaluated visually after the addition of 0.2 g of microencapsulated product to 200 ml of water having a temperature of 40°-45°C in a beaker. The dispersability is satisfactory when the microencapsulated particles are immediately wetted and a uniform dispersion is formed after 2 minutes of stirring. When viewed in a light microscope in transparency the dispersion consists of predominantly discrete particles.

The invention also relates to the use of microcapsules prepared by the process described above in pharmaceutical compositions, foods and feedstuffs and to an aqueous hydrocolloid suspension comprising a hydrophilic/aerophilic solid material, wherein the particle size of the solid material does not exceed 10  $\mu\text{m}$ , and preferably does not exceed 2  $\mu\text{m}$ , and wherein the suspension is free from wetting agents and is essentially free from organic solvents.

#### Example 1

1000 g of  $\beta$ -carotene was added in a  $\text{N}_2$ -atmosphere to a solution of 584 g of 240 Bloom gelatine and 100 g of Na-ascorbat in 2800 g of water having a temperature of 65°C. Before the addition of  $\beta$ -carotene the solution had been degassed using a vacuum and the pressure had been brought to equilibrium with  $\text{N}_2$ . When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. The milled suspension was transferred in a  $\text{N}_2$ -atmosphere to a degassed aqueous solution of 1300 g of gelatine and 2044 g of sucrose, wherein 9.5 g of ascorbyl palmitate and 14.3 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

The following intervals of product characteristics for four products were obtained:

$\beta$ -carotene content:	13.2 - 13.8 percent by weight
extractable $\beta$ -carotene:	0.3 - 0.8 percent by weight
absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}$ :	1.16
absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}$ :	14.7 - 15.2
stability after 6 months at 22°C:	100% of original $\beta$ -carotene content

The visual dispersability test was satisfactory.

#### Example 2

600 g of  $\beta$ -carotene was added in a  $\text{N}_2$ -atmosphere to a solution of 350 g of 240 Bloom gelatine and 60 g of Na-ascorbat in 1500 g of

water having a temperature of 65°C. Before the addition of  $\beta$ -carotene the solution had been degassed using a vacuum and the pressure had been brought to equilibrium with  $N_2$ . When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. The milled suspension was transferred to a degassed aqueous solution of 184 g of gelatine and 484 g of sucrose in a  $N_2$ -atmosphere, wherein 7.9 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

The following product characteristics were obtained:

$\beta$ -carotene content:	16.9	percent by weight
extractable $\beta$ -carotene:	0.4	percent by weight
absorption ratio $A_{452nm}:A_{483nm}$ :	1.16	
absorption ratio $A_{452nm}:A_{340nm}$ :	15.4	
stability after 3 months at 22°C:	98.7%	of original $\beta$ -carotene content

The visual dispersability test was satisfactory.

### Example 3

500 g of  $\beta$ -carotene was added to a solution of 146 g of 240 Bloom gelatine and 50 g of Na-ascorbat in 1000 g of water having a temperature of 65°C. When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. In the milled suspension 7.1 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

The following product characteristics were obtained:

$\beta$ -carotene content:	42.5	percent by weight
absorption ratio $A_{452nm}:A_{483nm}$ :	1.19	
absorption ratio $A_{452nm}:A_{340nm}$ :	10.3	

The visual dispersability test was satisfactory.

Example 4

5 360 g of  $\beta$ -carotene was added to a solution of 210 g of low Bloom  
gelatine and 36 g of Na-ascorbat in 935 g of water having a  
temperature of 65°C. When the  $\beta$ -carotene crystals were sufficiently  
wetted, the suspension was milled in a bead mill, DynoMill type KDL,  
10 during 1 hour of recirculation. The milled suspension was  
transferred to an aqueous solution of 648 g of high Bloom gelatine  
and 556 g of sucrose, wherein a mixture of 151 g of coconut oil and  
0.9 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified.  
After being thoroughly mixed the resulting suspension was spray  
cooled in a conventional manner.

15

The following product characteristics were obtained:

$\beta$ -carotene content:	11.3	percent by weight
extractable $\beta$ -carotene:	0.1	percent by weight
20 absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}$ :	1.16	
absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}$ :	14.8	
stability after 3 months at 22°C:	96.5%	of original $\beta$ -carotene content

25 The visual dispersability test was satisfactory.

Example 5

30 600 g of  $\beta$ -carotene was added in a  $N_2$ -atmosphere to a solution of  
350 g of 70 Bloom gelatine and 60 g of Na-ascorbat in 1500 g of  
water having a temperature of 65°C. Before the addition of  $\beta$ -caro-  
tene the solution had been degassed using a vacuum and the pressure  
had been brought to equilibrium with  $N_2$ . When the  $\beta$ -carotene cry-  
stals were sufficiently wetted, the suspension was milled in a bead  
35 mill, DynoMill type KDL, during 1 hour of recirculation. The milled  
suspension was transferred to a degassed aqueous solution of 592 g  
of 30 Bloom gelatine and 558 g of sucrose in a  $N_2$ -atmosphere,  
wherein a mixture of 117 g of coconut oil and 0.7 g of a mixture of  
 $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly

mixed the resulting suspension was subjected to a modified spray drying.

The following product characteristics were obtained:

5	$\beta$ -carotene content:	11.4	percent by weight
	extractable $\beta$ -carotene:	0.7	percent by weight
	absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}$ :	1.16	
	absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}$ :	14.4	
10	stability after 3 months at 22°C:	95.1%	of original $\beta$ -carotene content

The visual dispersability test was satisfactory.

15 Example 6

25 g of Canthaxanthin was added to a solution of 14.5 g of 106 Bloom gelatine and 2.5 g of Na-ascorbat in 70 g of water having a temperature of 65°C. When the cantaxanthin crystals were  
20 sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour. The milled suspension was transferred to an aqueous solution of 153 g of 240 Bloom gelatine and 153 g of sucrose, wherein 0.5 g of ascorbyl palmitate and 2.0 g of BHT and 10.0 g of ethoxyquin had been emulsified. After being  
25 thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

The final product contained 4.4 percent by weight of canthaxanthin.

30 The visual dispersability test was satisfactory.

Example 7

25 g of Astaxanthin was added to a solution of 14.5 g of 106 Bloom  
35 gelatine and 2.5 g of Na-ascorbat in 1500 g of water having a temperature of 65°C. When the astaxanthin crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour. The milled suspension was transferred to an aqueous solution of 153 g of 240 Bloom gelatine and 153 g of sucrose,

wherein 0.5 g of ascorbyl palmitate and 2.0 g of BHT and 10.0 g of ethoxyquin had been emulsified. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

5 The final product contained 4.5 percent by weight of astaxanthin.

The visual dispersability test was satisfactory.

#### Example 8

10

500 g of  $\beta$ -carotene was added to a solution of 250 g of gum arabic and 50 g of Na-ascorbat in 1750 g of water having a temperature of 65°C. When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1  
15 hour of recirculation. The milled suspension was transferred to an aqueous solution of 916 g of gum arabic and 780 g of sucrose, wherein 7.4 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

20

The following product characteristics were obtained:

$\beta$ -carotene content:	8.9	percent by weight
absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}$ :	1.16	
25 absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}$ :	14.2	

The visual dispersability test was satisfactory.

#### Example 9

30

500 g of  $\beta$ -carotene was added to a solution of 200 g of Methocel® E5 and 50 g of Na-ascorbat in 2000 g of water having a temperature of 65°C. When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1  
35 hour of recirculation. The milled suspension was transferred to an aqueous solution of 323 g of Methocel® E5 and 1224 g of sucrose, wherein 7.6 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly mixed the resulting suspension was subjected to a modified spray drying process in a conventional



manner.

The following product characteristics were obtained:

5	$\beta$ -carotene content:	4.0	percent by weight
	absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}:$	1.19	
	absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}:$	10.0	

The visual dispersability test was satisfactory.

10

#### Example 10

500 g of  $\beta$ -carotene was added to a solution of 500 g of Capsul® 50 g and of Na-ascorbat in 1500 g of water having a temperature of 65°C. When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. The milled suspension was transferred to an aqueous solution of 665 g of Capsul® and 777 g of sucrose, wherein 7.2 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been emulsified. After being thoroughly mixed the resulting suspension was subjected to a modified spray drying process in a conventional manner.

15

20

The following product characteristics were obtained:

25	$\beta$ -carotene content:	9.9	percent by weight
	absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}:$	1.16	
	absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}:$	13.6	

The visual dispersability test was satisfactory.

30

#### Example 11

500 g of  $\beta$ -carotene was added to a solution of 292 g of 240 Bloom gelatine in 1400 g of water having a temperature of 65°C. When the  $\beta$ -carotene crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. The milled suspension was transferred to an aqueous solution of 1132 g of 240 Bloom gelatine and 1298 g of sucrose, wherein 7.4 g of a mixture of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -tocopherol had been

35

emulsified. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

The following product characteristics were obtained:

5

$\beta$ -carotene content:	10.5	percent by weight
extractable $\beta$ -carotene:	0.3	percent by weight
absorption ratio $A_{452\text{nm}}:A_{483\text{nm}}$ :	1.17	
absorption ratio $A_{452\text{nm}}:A_{340\text{nm}}$ :	14.6	

10

The visual dispersability test was satisfactory.

#### Example 12

15 250 g of Ibuprofen was added to a solution of 146 g of 240 Bloom gelatine in 700 g of water having a temperature of 65°C. When the ibuprofen crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. The milled suspension was transferred to an aqueous  
20 solution of 566 g of 240 Bloom gelatine and 649 g of sucrose. After being thoroughly mixed the resulting suspension was spray cooled in a conventional manner.

The final product contained 12.9 percent by weight of ibuprofen.

25

#### Example 13

300 g of Curcumin crystals was added to a solution of 300 g of low-bloom gelatine and 300 g of sucrose in 900 g of water having a  
30 temperature of 65°C. When the curcumine crystals were sufficiently wetted, the suspension was milled in a bead mill, DynoMill type KDL, during 1 hour of recirculation. The milled suspension was transferred to a solution of 750 g of sucrose in 300 g of water. After being thoroughly mixed the resulting suspension was subjected  
35 to a modified spray drying process.

The final product contained 26.0 percent by weight of curcumin.

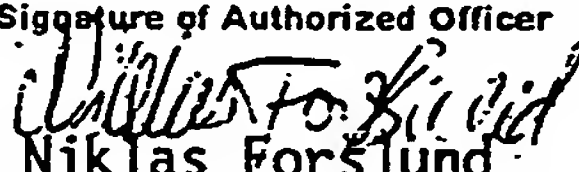
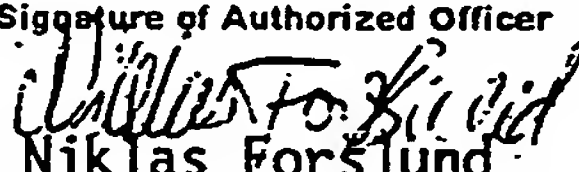
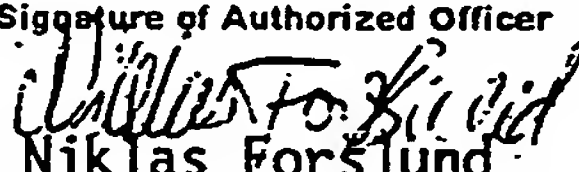
Claims

1. A process of preparing a hydrophobic/aerophilic solid which can be dispersed in water in the form of discrete microparticles, characterized in milling the solid in an aqueous medium in the presence of a hydrocolloid to obtain a suspension containing suspended particles of an average particle size not exceeding  $10\mu\text{m}$  and the suspension thus formed is finely divided and dried to obtain a powder.
2. A process according to claim 1, characterized in that the suspension containing suspended particles is finely divided and dried by spray cooling, conventional spray drying or modified spray drying.
3. A process according to claim 2, characterized in that the suspension is finely divided and dried in the presence of a spraying excipient.
4. A process according to any one of the preceding claims, characterized in that the solid is a carotenoid or derivative thereof.
5. A process according to claim 4, characterized in that the carotenoid is  $\beta$ -carotene,  $\beta$ -apo-8'-carotenal, canthaxanthin, and/or astaxanthin.
6. A process according to claims 1-3, characterized in that the solid is a natural colorant.
7. A process according to claim 6, characterized in that the natural colorant is curcumin, chlorophyll and/or carmine.
8. A process according to claims 1-3, characterized in that the solid is a drug.
9. A process according to claim 8, characterized in that the drug is ibuprofen, griseofulvin, a benzodiazepine, phenacetin and/or a hormone.

10. A process according to any one of the preceding claims, characterized in that the hydrocolloid is gelatine, gum arabic, soya bean protein and/or modified starch.
- 5 11. A process according to any one of the preceding claims, characterized in that the suspension contains a carbohydrate, in an amount of up to 70 percent by weight of the suspension.
- 10 12. A process according to claim 11, characterized in that the carbohydrate is sucrose.
13. A process according to any one of the preceding claims, characterized in that the suspension further contains  
15 an antioxidant.
14. A microencapsulated product containing a hydrophobic/aerophilic solid material having a maximum average particle size not exceeding 10 $\mu$ m and which can be dispersed in water in the form  
20 of discrete microparticles, characterized in that the amount of solid active material in the microencapsulated product is from 22 to 71 percent by weight.
15. Use of microcapsules prepared by the process according to claim  
25 1 in pharmaceutical compositions, foods and feedstuffs.
16. An aqueous hydrocolloid suspension comprising a hydrophobic/aerophilic solid material characterized in that the particle size of the solid material does not exceed 10  $\mu$ m, and  
30 preferably does not exceed 2  $\mu$ m, and that the suspension is free from wetting agents and essentially free from organic solvents.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 90/00278

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC5: A 61 K 9/50, 9/10, 9/14, B 01 J 13/02, A 23 L 1/30</b>																				
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched<sup>7</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border: 1px solid black; text-align: left; padding: 2px;">Classification System</th> <th style="border: 1px solid black; text-align: left; padding: 2px;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">IPC5</td> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">A 61 K; B 01 J; A 23 L</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched<sup>8</sup></div> <p style="padding: 5px 0;">SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	A 61 K; B 01 J; A 23 L														
Classification System	Classification Symbols																			
IPC5	A 61 K; B 01 J; A 23 L																			
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border: 1px solid black; text-align: left; padding: 2px;">Category *</th> <th style="border: 1px solid black; text-align: left; padding: 2px;">Citation of Document,<sup>11</sup> with indication, where appropriate, of the relevant passages<sup>12</sup></th> <th style="border: 1px solid black; text-align: left; padding: 2px;">Relevant to Claim No.<sup>13</sup></th> </tr> <tr> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">X</td> <td style="border: 1px solid black; padding: 5px;">Dialog Information Services, File 350: World Patent Index 1963-1980, WPI Acc No: 78-4130A/26 &amp; RD,A, 170064 (ANONYMOUS) 10 June 1978, abstract --</td> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">1-5, 10</td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">P,X</td> <td style="border: 1px solid black; padding: 5px;">EP, A1, 0347751 (HOFFMAN-LA ROCHE AG) 27 December 1989, see column 1, line 1 - column 2, line 36; claims 1-10 --</td> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">1-8,10-12</td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">X</td> <td style="border: 1px solid black; padding: 5px;">US, A, 3529065 (H W FLANDREAU JR) 15 September 1970, see column 1, line 53 - column 2, line 60; claims 1-4 --</td> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">1-3,8</td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">X</td> <td style="border: 1px solid black; padding: 5px;">DE 1617737 (PFIZER INC) 9 March 1972, see the whole document --</td> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">1-3,6,8, 10,11, 13,15</td> </tr> <tr> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">Y</td> <td style="border: 1px solid black; padding: 5px;">--</td> <td style="border: 1px solid black; vertical-align: top; padding: 5px;">4-5,7,9, 14,16</td> </tr> </table>			Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	Dialog Information Services, File 350: World Patent Index 1963-1980, WPI Acc No: 78-4130A/26 & RD,A, 170064 (ANONYMOUS) 10 June 1978, abstract --	1-5, 10	P,X	EP, A1, 0347751 (HOFFMAN-LA ROCHE AG) 27 December 1989, see column 1, line 1 - column 2, line 36; claims 1-10 --	1-8,10-12	X	US, A, 3529065 (H W FLANDREAU JR) 15 September 1970, see column 1, line 53 - column 2, line 60; claims 1-4 --	1-3,8	X	DE 1617737 (PFIZER INC) 9 March 1972, see the whole document --	1-3,6,8, 10,11, 13,15	Y	--	4-5,7,9, 14,16
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>																		
X	Dialog Information Services, File 350: World Patent Index 1963-1980, WPI Acc No: 78-4130A/26 & RD,A, 170064 (ANONYMOUS) 10 June 1978, abstract --	1-5, 10																		
P,X	EP, A1, 0347751 (HOFFMAN-LA ROCHE AG) 27 December 1989, see column 1, line 1 - column 2, line 36; claims 1-10 --	1-8,10-12																		
X	US, A, 3529065 (H W FLANDREAU JR) 15 September 1970, see column 1, line 53 - column 2, line 60; claims 1-4 --	1-3,8																		
X	DE 1617737 (PFIZER INC) 9 March 1972, see the whole document --	1-3,6,8, 10,11, 13,15																		
Y	--	4-5,7,9, 14,16																		
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p><b>* Special categories of cited documents: <sup>10</sup></b></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the International filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																				
<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;">           Date of the Actual Completion of the International Search   <b>4th February 1991</b> </td> <td style="width: 50%; border: 1px solid black; padding: 5px;">           Date of Mailing of this International Search Report   <b>1991 -02- 05</b> </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; vertical-align: bottom;">           International Searching Authority   <div style="text-align: center;"><b>SWEDISH PATENT OFFICE</b></div> </td> <td style="border: 1px solid black; padding: 5px; vertical-align: bottom;">           Signature of Authorized Officer  <div style="text-align: center;">   <b>Niklas Forslund</b> </div> </td> </tr> </table>			Date of the Actual Completion of the International Search  <b>4th February 1991</b>	Date of Mailing of this International Search Report  <b>1991 -02- 05</b>	International Searching Authority  <div style="text-align: center;"><b>SWEDISH PATENT OFFICE</b></div>	Signature of Authorized Officer <div style="text-align: center;">   <b>Niklas Forslund</b> </div>														
Date of the Actual Completion of the International Search  <b>4th February 1991</b>	Date of Mailing of this International Search Report  <b>1991 -02- 05</b>																			
International Searching Authority  <div style="text-align: center;"><b>SWEDISH PATENT OFFICE</b></div>	Signature of Authorized Officer <div style="text-align: center;">   <b>Niklas Forslund</b> </div>																			

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A2, 0074050 (BASF AG) 16 March 1983, see page 3, line 15 - page 5, line 35 --	1-5,8, 10-13
X	GB, A, 2122085 (FREUND INDUSTRIAL CO LTD) 11 January 1984, see claims 1-6 --	16
X	EP, A, 0333523 (THE UAB RESEARCH CORPORATION). 20 September 1989, see page 2, line 28 - page 3, line 8; claims 1-53 examples --	14
X	US, A, 4726955 (D HORN ET AL) 23 February 1988, see column 3, line 65 - column 4, line 2; claims 1-4 A	16  1-15
	-- -----	



**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 90/00278**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the Swedish Patent Office EDP file on **90-12-28**  
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0347751	89-12-27	AU-D- JP-A-	3657389 2051594 90-01-04 90-02-21
US-A- 3529065	70-09-15	CH-A- DE-A- FR-A- GB-A- NL-A-	502773 1767342 1578902 1178369 6806050 71-02-15 72-03-09 69-08-22 70-01-21 68-11-04
DE- - 1617737	72-03-09	BE-A- FR-A- GB-A- NL-A- US-A-	701557 1544697 1178622 6709998 3526682 68-01-19 00-00-00 70-01-21 68-02-26 70-09-01
EP-A2- 0074050	83-03-16	CA-A- DE-A- JP-A- US-A-	1188572 3135329 58055412 4519961 85-06-11 83-03-24 83-04-01 85-05-28
GB-A- 2122085	84-01-11	CH-A- DE-A-C- GB-A-B- JP-A- US-A- JP-C- JP-A- JP-B- JP-C- JP-A- JP-B-	646052 3013839 2050828 55139319 4540602 1322043 55167218 60024768 1257654 55167219 58007609 84-11-15 80-10-30 81-01-14 80-10-31 85-09-10 86-06-11 80-12-26 85-06-14 85-03-29 80-12-26 83-02-10
EP-A- 0333523	89-09-20	AU-D- WO-A-	3343389 89/08449 89-10-05 89-09-21
US-A- 4726955	88-02-23	DE-A- EP-A-	3611229 0239949 87-10-08 87-10-07

**THIS PAGE BLANK (USPTO)**

**This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record.**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**